

glacial acetic acid. The reaction was exothermic. The mixture was allowed to stand at room temperature for five days and then the excess peroxide was decomposed with platinum black. After filtration, the reaction mixture was distilled to dryness in a vacuum still below 50°. Sixty-seven mg. of crude solid material was obtained, which was recrystallized once from carbon tetrachloride and five times from alcohol to yield a white crystalline compound, m. p. 93.6–94° (cor.).

*Anal.*³ Calcd. for C₈H₁₀SO₄: C, 36.15; H, 6.07; S, 19.26. Found: C, 36.27; H, 5.93; S, 18.75.

The same compound was obtained when a trace of ammonium molybdate was used as catalyst in the oxidation.

A determination of the molecular weight by the Rast micro method gave 170; the calculated value for C₈H₁₀SO₄ is 166.

The saponification equivalent of the compound was determined using an ethylene glycol solution of potassium hydroxide.⁹

Anal. Calcd. for C₈H₁₀SO₄: sapon. equiv., 166. Found: sapon. equiv., 178.3, 178.5.

Preparation of Methyl β-Methylthiolpropionate.—A solution of sodium methylate, prepared by dissolving 2.85 g. sodium (0.124 atom) in 30 cc. of absolute methyl alcohol, was placed in an ice-cooled three-necked flask, equipped with reflux condenser, mercury-sealed stirrer and dropping funnel, and a cooled solution of 5.95 g. (0.124 mole) of methyl mercaptan in 25 cc. of absolute methyl alcohol

was added gradually. The mixture was then gradually heated to boiling, a solution of 20.7 g. (0.124 mole) of methyl β-bromopropionate in absolute methyl alcohol slowly added, and the solution was refluxed for an hour. After dilution with water, the solution was extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and the ether was removed by distillation on the water-bath. A yield of 9.1 g. (54.7% yield) of methyl β-methylthiolpropionate boiling at 69° at 11 mm. was thus obtained.

Oxidation of Methyl β-Methylthiolpropionate.—One and a half grams of methyl β-methylthiolpropionate was oxidized by the method used for the pineapple compound, except that approximately 5 mg. of ammonium molybdate was used as catalyst, and the mixture was allowed to stand for only three hours. After three recrystallizations from ethyl alcohol-water, white needles melting at 94–94.6° were obtained. A mixed m. p. with the oxidized pineapple compound showed no depression.

Anal. Calcd. for C₈H₁₀SO₄: C, 36.15; H, 6.07; S, 19.26. Found: C, 36.24; H, 6.10; S, 18.73, 18.83.

Summary

A sulfur-containing ester, CH₃SCH₂CH₂COO-CH₃, has been isolated from the higher-boiling volatile material from pineapple fruit pulp. This compound has been converted by oxidation to the sulfone, m.p. 93.6–94°, which was identified by synthesis.

PASADENA, CALIFORNIA

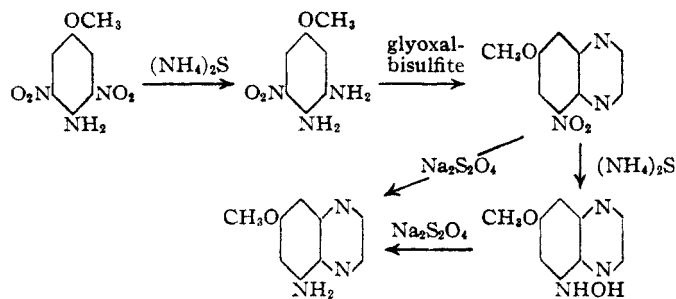
RECEIVED JULY 11, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

Syntheses in the Quinoxaline Series. Preparation of 7-Methoxy-5-aminoquinoxaline and 7-Methoxy-5-hydroxylaminoquinoxaline

BY R. H. MIZZONI AND PAUL E. SPOERRI

The literature of quinoxaline derivatives is surprisingly meager in view of the potential usefulness of some of them as medicinals. It was thought that certain compounds which were structurally analogous to the plasmochin type might possess useful properties. This investigation necessitated the preparation and characterization of 7-methoxy-5-amino-quinoxaline, along with several hitherto unknown intermediates.



Gawron and Spoerri¹ have prepared 7-methoxy-5-aminoquinoxaline through condensation of 3,4,5-triaminoanisole with glyoxal-bisulfite. In the

(1) Gawron and Spoerri, *THIS JOURNAL*, **67**, 514 (1945).

present investigation the synthesis was accomplished through the condensation of 3,4-diamino-5-nitroanisole with glyoxal-bisulfite and subsequent reduction of the resulting 7-methoxy-5-nitroquinoxaline. The accompanying flow chart, starting with 3,5-dinitro-4-aminoanisole, shows the reactions involved in this synthesis.

3,5-Dinitro-4-aminoanisole was prepared according to the method of Reverdin² by nitration of *m*-nitrobenzenesulfonyl-*p*-aminoanisole. *m*-Nitrobenzenesulfonyl chloride was prepared by known methods.³

Reduction of 3,5-dinitro-4-aminoanisole with ammonium sulfide gave the desired 3,4-diamino-5-nitroanisole, while with sodium sulfide only resin formation resulted. The compound is weakly basic, its hydrochloride reverting to the free base at the melting point of the base. The hydrochloride is readily hydrolyzed in warm acetone and in warm ethyl methyl ketone. The amine could not be acetylated by any of the usual means, nor did it form a picrate.

(2) Reverdin, *Ber.*, **42**, 1525 (1909); *ibid.*, **45**, 349 (1912).

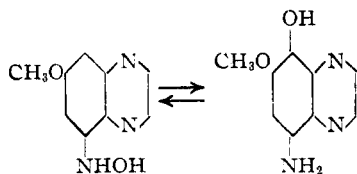
(3) German Patent 89,997 (1896).

Condensation of 3,4-diamino-5-nitroanisole was attempted with glyoxal and with glyoxal-bisulfite. In the first case very little product was isolated, the reaction being characterized by resin formation. The condensation was more favorable with glyoxal-bisulfite, however, 7-methoxy-5-nitroquinoxaline being obtained. This compound, occurring as brown needles from alcohol, is insoluble in dilute acids, although it dissolves readily in concentrated hydrochloric acid. The lack of basicity is no doubt due to influence of the nitro group.

A variety of reduction methods were employed on 7-methoxy-5-nitroquinoxaline. Vigorous reducing agents, tin, zinc, and iron, in acid media, gave only resinous products. Catalytic reduction in glacial acetic acid gave similar results. Reduction in neutral solution with zinc and ammonium chloride yielded 7-methoxy-5-aminoquinoxaline. Similar results were obtained with sodium hydrosulfite. Alkaline reduction showed some interesting results. Zinc and sodium hydroxide yielded 7-methoxy-5-aminoquinoxaline, while reduction with ammonium sulfide gave 7-methoxy-5-hydroxylaminoquinoxaline.

The 7-methoxy-5-aminoquinoxaline sublimes quite readily at reduced pressure. In this regard it resembles analogous compounds of the quinoline series. The compound forms a dihydrochloride by the addition of excess methanolic hydrogen chloride to the amine in methanol. The salt crystallizes with one molecule of methanol in the form of pinkish-white needles, and is obtained anhydrous as dark maroon crystals. The amine is acetylated with great ease. It can be diazotized quantitatively with nitrous acid, thus behaving like an aromatic amine.

The hydroxylamino compound obtained from 7-methoxy-5-nitroquinoxaline on reduction with ammonium sulfide has some interesting properties. It may be reduced with sodium hydrosulfite to the corresponding amino compound. It is soluble in dilute hydrochloric acid, and in 15% sodium hydroxide, denoting the presence of both acidic and basic groups. A possible explanation of its acidic character may be formulated, that the compound exists in equilibrium with the tautomeric *p*-aminophenol.



The compound decomposes at its melting point. It reduces both ammoniacal silver oxide and silver nitrate, but not Fehling solution, and reacts mole for mole with nitrous acid. Unlike β -phenylhydroxylamine, it does not condense with benzaldehyde to give the corresponding nitron.

All melting points are corrected. The micro-

analyses were performed by Mr. Wm. Saschek of the College of Physicians and Surgeons of Columbia University, and by the Arlington Laboratories, Arlington, Va.

Experimental

3,4-Diamino-5-nitroanisole.—One hundred and twenty-four grams (0.58 mole) of 3,5-dinitro-*p*-anisidine was suspended in a mixture of 1200 ml. of denatured alcohol and 600 ml. of 28% ammonium hydroxide. The mixture was heated to 60°, and a rapid stream of hydrogen sulfide was admitted during one and one-half hours. During this time the product separated out. The reaction mixture was allowed to remain overnight in the refrigerator. The dark red product was filtered off and allowed to air-dry, then taken up in 1500 ml. of boiling 10% hydrochloric acid. The acid solution was filtered hot through a large, open-textured filter. The solution was reheated, then made strongly alkaline with 28% ammonium hydroxide. The precipitated material was filtered off, washed thoroughly with water, and dried *in vacuo*; yield 56.5 g. (53.1%), m. p. 184–184.5°.

Anal. Calcd. for $C_7H_7ON_3$: C, 45.90; H, 4.95. Found: C, 45.91; H, 4.86.

7-Methoxy-5-nitroquinoxaline.—Fifty-two grams (0.28 mole) of 3,4-diamino-5-nitroanisole was suspended in 4 liters of water, and the mixture was heated to 80° with rapid stirring. One hundred and four grams (0.39 mole) of glyoxal-bisulfite (Carbide and Carbon) was added all at once to the reaction mixture. The reaction mixture was allowed to stir rapidly at 80–90° for three hours. The solution was filtered hot, then set aside to cool. The cold solution was made distinctly alkaline with 25% sodium hydroxide, and the light-tan colored product separated out. This material was filtered off and washed well with water, then dried *in vacuo*; yield 15.5 g. (26.8%), m. p. 178–180°.

The 7-methoxy-5-nitroquinoxaline was recrystallized from boiling alcohol; yield 15.0 g. (25.8%), m. p. 182.5–183°.

Anal. Calcd. for $C_9H_7ON_3$: C, 52.80; H, 3.45. Found: C, 52.50; H, 3.52.

7-Methoxy-5-hydroxylaminoquinoxaline.—Eight grams (0.039 mole) of 7-methoxy-5-nitroquinoxaline was suspended in a mixture of 60 cc. of denatured alcohol and 125 cc. of 28% ammonium hydroxide; the material was allowed to dissolve, with stirring, as much as possible. A rapid stream of hydrogen sulfide was passed through the solution at room temperature during one-half hour. During the reaction the temperature rose to 35°. The reaction mixture was set aside in the refrigerator for twenty-four hours. The solution was filtered and the solid product recrystallized twice from alcohol. The resulting crystals were dried *in vacuo*; yield 2.8 g. (0.015 mole), m. p. 157° dec.

Anal. Calcd. for $C_9H_9O_2N_3$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.52; H, 4.79; N, 21.56.

Nitrosation of 7-Methoxy-5-hydroxylaminoquinoxaline.—Twenty-two and one-tenth milligrams (0.116 millimole) of the 5-hydroxylamino compound was dissolved in dilute hydrochloric acid and titrated at 5° with 0.1000 *M* sodium nitrite. One-tenth molar sodium nitrite required 1.14 ml. (0.114 millimole).

7-Methoxy-5-aminoquinoxaline.—Four grams of 7-methoxy-5-nitroquinoxaline was dissolved in 280 ml. of boiling alcohol. To this boiling solution on a water-bath there was added 16 g. of sodium hydrosulfite in 60 ml. of water. The mixture was heated for one-half hour, then cooled and diluted with 500 ml. of water. The solution was extracted with four 250-ml. portions of ether. The ether extracts were washed once with 100 ml. of water, and the washing was extracted once with 100 ml. of ether. The combined ether extracts were distilled to a small volume, the residue transferred to a glass crystallizing dish, evaporated almost to dryness on the water-bath, and dried *in*

vacuo. The dried material was sublimed at 0.005–0.02 mm. and 80–90°; yield 1.5 g. (44.1%), m. p. 96.5–96.7°.

Anal. Calcd. for $C_9H_9ON_3$: C, 61.70; H, 5.18; N, 23.98. Found: C, 61.45; H, 5.18; N, 24.07.

Diazotization of 7-Methoxy-5-aminoquinoxaline.—Twenty-three and one-tenth milligrams (0.132 millimole) of the amino compound was dissolved in dilute hydrochloric acid, and titrated at 5° with 0.1000 molar sodium nitrite. One-tenth molar sodium nitrite required 1.32 ml. (0.132 millimole).

7-Methoxy-5-acetaminoquinoxaline.—About 5 mg. of 7-methoxy-5-aminoquinoxaline was dissolved in several drops of acetic anhydride. After shaking for two minutes at room temperature, the mixture was diluted with several milliliters of water and shaken. The white needles which separated were filtered off, washed with water, and recrystallized from 30% alcohol; m. p. 173.7–174.5°.

7-Methoxy-5-aminoquinoxaline Dihydrochloride.—About one hundred milligrams of 7-methoxy-5-aminoquinoxaline was dissolved in 10 ml. of methanol. To this there was added a considerable excess of 10 *N* methanolic hydrogen chloride over that theoretically required for the trihydrochloride. On evaporation of the solvent at room temperature with the aid of a current of dry air, pinkish-white crystals separated out. The hydrochloride was dried *in vacuo*; m. p. 205–208°.

Anal. Calcd. for $C_9H_9ON_3 \cdot 2 HCl \cdot (CH_3OH)$: Cl, 26.04. Found: Cl, 25.97.

About one hundred milligrams of 7-methoxy-5-amino-

quinoxaline was dissolved in 10 ml. of methanol. To this there was added a considerable excess of 10 *N* methanolic hydrogen chloride over that theoretically required for the trihydrochloride. On évaporation of the solvent on a water-bath a maroon colored substance was obtained. This substance was dried *in vacuo*; m. p. 210.5–211°.

Anal. Calcd. for $C_9H_9ON_3 \cdot 2 HCl$: Cl, 28.83. Found: Cl, 28.88.

Summary

1. 3,4-Diamino-5-nitroanisole was prepared by alkaline reduction of 3,5-dinitro-4-aminoanisole.

2. 7-Methoxy-5-nitroquinoxaline was synthesized by condensation of 3,4-diamino-5-nitroanisole with glyoxal-bisulfite.

3. 7-Methoxy-5-aminoquinoxaline was prepared by reduction of 7-methoxy-5-nitroquinoxaline.

4. 7-Methoxy-5-hydroxylaminoquinoxaline was synthesized by alkaline reduction of 7-methoxy-5-nitroquinoxaline.

5. A number of the properties of these four compounds are described.

BROOKLYN 2, N. Y.

RECEIVED APRIL 6, 1945

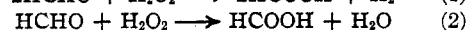
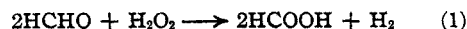
The Action of Hydrogen Peroxide on Carbohydrates¹

BY JOHN H. PAYNE² AND LUTHER FOSTER³

Simple carbohydrates, such as *d*-glucose, are known to be oxidized by hydrogen peroxide. Numerous investigators^{4,5,6} have proposed reaction mechanisms based upon products isolated under various conditions of temperature, concentration, and catalysts. There have been few attempts to consider the reaction quantitatively, although Evans and co-workers⁷ have made a thorough study of the quantitative oxidation of certain sugars with silver oxide.

The experimental method of Fry and Payne⁸ which makes possible the quantitative correlation of the extent of the occurrence of the likely reactions with the amounts of hydrogen peroxide used, has given insight to the reaction mechanism in the case of many simple organic compounds.⁹ The outstanding characteristic of the reaction of hydrogen peroxide with many of the compounds is the liberation of relatively large quantities of hydrogen. Payne and Lemon⁹ demonstrated that the hydrogen did not have its source in the aldehyde group. They proposed that any compound

giving formaldehyde as an intermediate product might be expected to yield hydrogen when treated with hydrogen peroxide. The quantity of hydrogen produced would depend upon the quantity of formaldehyde formed, and, as found by Fry and Payne,⁸ upon the concentration of the hydrogen peroxide. Higher concentrations of hydrogen peroxide might be expected to cause more extensive oxidation and hence produce more formaldehyde. Of the two concurrent reactions



however, (2) predominates at higher peroxide concentrations, so that less hydrogen would result from the formaldehyde. Thus in the case of the carbohydrates where stepwise oxidation should result in the formation of formaldehyde at the last step, the total quantity liberated depends upon both the extent of the degradation and the concentration of hydrogen peroxide present when the formaldehyde step is reached. Of course the scission of formaldehyde, as found by Evans and co-workers,⁷ may occur at initial or subsequent stages.

In order to determine the extent to which the liberation of hydrogen characterizes the reaction of hydrogen peroxide with carbohydrates, a quantitative investigation was conducted with glyceric aldehyde, erythritol, *d*-arabinose, and *d*-glucose in order to complete the one to six car-

(1) The experimental work was performed while the authors were at the University of Hawaii.

(2) Pacific Chemical and Fertilizer Company, Honolulu, Hawaii.

(3) Brown University, Providence, R. I.

(4) Bernhauer and Nistler, *Biochem. Z.*, **205**, 230 (1929).

(5) Kuen, *ibid.*, **215**, 12 (1929).

(6) Kuchlin, *Rec. trav. chim.*, **51**, 887 (1932).

(7) Bush, Clark, Genung, Schroeder and Evans, *J. Org. Chem.*, **1**, 1 (1936).

(8) Fry and Payne, *THIS JOURNAL*, **53**, 1973 (1931).

(9) Payne and Lemon, *ibid.*, **63**, 226 (1941).